REMARKS/ARGUMENTS

35 U.S.C. 112

Claim 8 has been amended to delete the second recited range, and this has been presented as new claim 10. Accordingly, the indefiniteness rejection under 35 U.S.C. 112 has been overcome.

35 U.S.C. 103

The examiner has cited the prior art document Shefter et al (US 2002/0032166 A1) ("*Shefter*"), and has rejected claims 2, 4-7 and 9 as being obvious with respect to this prior art document. *Shefter* describes a method for preparing homogeneous particles containing a pharmaceutical substance which is not normally soluble in a homogenous way. Improved solubilisation/distribution is obtained using a hydrophobic ion pair complex between the pharmaceutical substance and an amphiphillic material (Abstract).

Shefter teaches that enzymes can be formulated into such homogenous particles using this method and that such particles can be administered to patients. As pointed out by the examiner, the authors in *Shefter* believe that such particles could be administered via the pulmonary tract.

The basis of the examiner's obviousness rejection can be summarised as follows: the examiner believes that since *Shefter* states that the homogenous particles can comprise an organic solvent such as 1-octanol, a particle comprising 1-octanol for pulmonary administration to a patient suffering from cystic fibrosis would be expected to have the same effect as compositions administered according to the method of claim 9. The examiner's rejection therefore takes two related forms, (i) *Shefter* inherently discloses a composition/method within the scope of claim 9; and (ii) *Shefter* renders the method of claim 9 obvious because of this inherent disclosure.

The examiner's analysis of *Shefter* excludes several key features, and when the complete contents of this prior art document are considered, the feature of 1-octanol is not necessarily present in the methods and formulations alluded to in this document. Therefore, one of ordinary skill in the art could not have arrived at the method of claim 9.

The Court of Appeals for the Federal Circuit has indicated that in the analysis of inherent disclosures, if a feature is to be considered inherent this means that the feature must be "necessarily present" and not merely sometimes, occasionally, or possibly present.

This is not the case for the use of 1-octanol as an organic solvent in *Shefter*. 1-octanol is just one example of an organic solvent which could be used to implement the solubilisation method described therein. For instance at paragraph [0066] *Shefter* states:

> [0066] The organic solvent may be any organic liquid in which the pharmaceutical substance and the amphiphilic material, together, are soluble, such as in the form of an HIP complex. The following is a non-limiting, representative list of some organic solvents, with specific exemplary solvents listed in parentheses, which may be used with the present invention: monohydric alcohols (methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 1-hexanol, 1-octanol, trifluoroethanol); polyhydric alcohols (propylene glycol, PEG 400, 1,3-propanediol); ethers (tetrahydrofuran (THF), diethyl ether, diglyme); alkanes (decalin, isooctane, mineral oil); aromatics (benzene, toluene, chlorobenzene, pyridine); amides (n-methyl pyrrolidone (NMP), N,N-dimethylformamide (DMF)); esters (ethyl acetate, methyl acetate); chlorocarbons (CH_2Cl_2, $CHCl_3$, CCl_4, 1,2-dichloroethane); and others such as nitromethane, acetone, ethylene diamine, acetonitrile, and trimethyl phosphate.

The use of organic solvents to solubilise, water insoluble compounds and so place them into aqueous solution has been known since the conception of modern chemistry from the early 1900s onwards.

In *Shefter*, the organic solvent is not an essential aspect of the invention described therein. Instead, *Shefter* concerns 'substances for' and 'methods of' placing a normally insoluble pharmaceutical substance into a homogenous solution for instance in an organic solvent. The organic solvent is not important *per se*, hence the large list of possible organic solvents which can be used.

An inherent disclosure from a prior art reference must flow naturally from the prior art reference (*In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981). An inherent disclosure of a treatment method according to claim 9, which involves the administration of at least one linear n-alkanol (C_6-C_{10}) to a patient suffering from cystic fibrosis, does not flow naturally from *Shefter* as out of the large number of possible organic solvents discussed in Shefter no reason is given why the skilled man should have chosen 1-octanol.

As explained above *Shefter* is concerned with preparing particles which comprise a homogenous distribution of a pharmaceutically active substance. Among many other examples of such compounds *Shefter* describes the possibility (no experimental data is provided) of placing the enzyme DNase into appropriately sized particles and then administering these to a patient who has cystic fibrosis. DNase is a well known medicament for treating cystic fibrosis and is used to thin and liquefy mucus in the lungs of patients with cystic fibrosis.

One possible use of the solubilisation method described in *Shefter* therefore concerns preparing DNase containing particles, in which the DNase is uniformly distributed.

Several important failures in the teaching of *Shefter* must be pointed out however:

- *Shefter* does not predict or experimentally show the effects of a composition made according to *Shefter* which comprises DNase and an organic solvent such as 1-octanol upon the lungs of cystic fibrosis patients.

- *Shefter* does not teach a particular composition or treatment regime for cystic fibrosis which comprises only 1-octanol.

Therefore since *Shefter* does not provide any actual relevant embodiments, *Shefter* lacks enablement for those aspects of the present invention which the examiner believes to be inherently disclosed by *Shefter*. Given this lack of enablement in accordance with Schering Corp. v. Geneva Pharm., 68 USPQ 1760, 1763 (Fed. Cir. 2003; M.P.E.P. 2111.04),*Shefter* can not inherently disclose the present invention.

We do not understand the basis for the examiner's conclusion (page 6, lines 10 to 17 of the Office Action) that a composition comprising DNase made according to Example 15 of *Shefter* would, following administration to a patient, generate in the vicinity of their epithelial cell membranes a concentration greater than those specified for instance in claim 8. First,

Example 15 concerns insulin (a 51 amino acid peptide hormone), not DNase (a 282 amino acid enzyme (human DNase I)) and these two substances can not be considered interchangeable in a protocol on a like for like basis. Assuming DNase could be dissolved using a HIP complex and precipitated according to the scant method described in Example 15, then resuspended in an organic solvent, example 15 does not describe the final concentration of insulin following resuspension. Also *Shefter* does not describe a protocol to administer a Dnase solution to a patient in need thereof.

Therefore, we do not see how the final concentration of an organic solvent can be predicted in an unknown patient following the administration for an unknown period of time via an unknown method of an unknown composition comprising an unknown concentration of DNase and also comprising an unknown concentration of an organic solvent.

Commercially available DNase solutions, such as Pulmozyme®, do not comprise any organic solvents and in particular do not comprise 1-octanol. The proposed use of an organic solvent in Shefter to generate solutions of DNase has therefore not been adopted by the relevant sections of the healthcare industry, for reasons we can not know but could include the fact that the proposed system of Shefter does not in fact allow DNase to be placed into solution as the inventors therein predict but do not prove. We enclose the product information for Pulmozyme®, which lists the ingredients of the administered aqueous solution as being 1.0 mg/ml DNase, 8.77 mg/ml calcium chloride dehydrate and 8.77 mg/ml sodium chloride.

To reiterate our arguments, *Shefter* does not disclose any method which involves the administration of a linear n-alkanol to a patient suffering from cystic fibrosis. *Shefter* does disclose the possibility of making a better DNase composition using an organic solvent such as 1-octanol, but does not detail the concentration of either the active agent DNase or the organic solvent in such an improved composition, nor does it detail a method to administer such a composition to a patient in need thereof. Finally, commercially available DNase compositions such as Pulmozyme® do not comprise any organic solvent. *Shefter* can not therefore be considered to inherently disclose the method according to claim 9.

Amendments to claim 9

In order to further the prosecution of this Patent Application, claim 9 has been amended to substitute the transitional phrase "consisting of" for "comprising". The method of amended claim 9 now consists exclusively of the administration of the specified linear n-alkanol to a patient in need thereof. Therefore, a method involving the administration of a combination of a linear n-alkanol and Dnase is excluded from this method, further differentiating the present invention from *Shefter*.

Concerning the broader question of whether the present invention and specifically the method of claim 9 is obvious with respect to *Shefter*, as a first point, one of ordinary skill in the art starting with *Shefter* and seeking to formulate a treatment regime for cystic fibrosis would inherently base their regime on Dnase. Therefore one of ordinary skill in the art, starting with *Shefter* which only discusses one (already known and proven) treatment for cystic fibrosis would formulate a treatment regime using this enzyme. More specifically one of ordinary skill in the art would not have been motivated to formulate a treatment method as per claim 9 as now presented which does not include DNase administration.

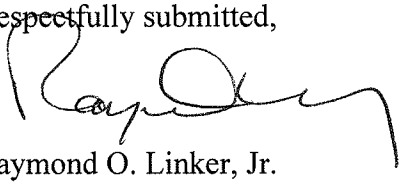
In accordance with In re Merck & Co., Inc., 800 F.2d 1091 (Fed. Cir. 1986), the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success on the part of one skilled in the art to do so. In the present situation, there can be no expectation of success as one of ordinary skill in the art would not have been aware that 1-octanol alone when administered to the lungs of a cystic fibrosis patient could have a beneficial effect, and would have found no reason to expect success based upon *Shefter* given the absence of any teaching or experimental evidence to suggest that this was the case.

Therefore in the absence of such an expectation of success, the method according to claim 9 would not have been obvious to one skilled in the art having reference to *Shefter*.

In view of the foregoing remarks, it is respectfully submitted that the rejections under 35 U.S.C. 102(a) have been overcome. Formal notification of the allowability of all claims as now presented is respectfully solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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